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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/817,448	DEES ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *41-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-40 and 46-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-50* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group 1, claims 1-40 and 46-50, without traverse, filed 8/6/02 in Paper No. 7 is acknowledged and has been entered. Claims 41-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention. Currently, claims 1-50 are pending and claims 1-40 and 46-50 are under examination.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Also, the current status, i.e. US Patent Number, Abandoned, of all nonprovisional parent applications referenced should be included.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-28, 30-40 and 46-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting, "useful for high energy therapeutic treatment, because the term "useful" is a subjective term that lacks a comparative basis for defining its metes and bounds.

In claims 2-15, "Claim" should be --claim--.

Claim 11 is vague and indefinite in reciting, "useful for the treatment of indications ...consisting of conditions affecting ..." because it is unclear as recited what is encompassed by the term "indications" and how it relates functionally with the term "conditions". Further, it is unclear what is encompassed by the term "affecting" as used in the claim and the term "useful" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Regarding claim 11, the phrase "related organs" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "related organs"), thereby rendering the scope of the claim unascertainable.

Claim 16 provides for the use of a halogenated xanthene, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 16-28 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under

35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 17 is vague and indefinite in reciting, "for the treatment of indications ...consisting of conditions affecting ..." because it is unclear as recited what is encompassed by the term "indications" and how it relates functionally with the term "conditions". Further, it is unclear what is encompassed by the term "affecting" as used in the claim.

Regarding claim 17, the phrase "related organs" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "related organs"), thereby rendering the scope of the claim unascertainable.

In claims 17-21, "Claim" should be --claim--.

Claim 17 is vague and indefinite in reciting, "treatment of indications ...consisting of conditions" because it is unclear as recited what is encompassed by the term "indications" and how it relates functionally with the term "conditions".

Claim 22 is vague and indefinite in reciting, "therapeutically effective amount" because the phrase "therapeutically effective" is a subjective phrase that lacks a comparative basis for defining its metes and bounds.

In claims 23-28, "Claim" should be --claim--.

In claims 30-40, "Claim" should be --claim--.

Claim 46 is vague and indefinite in reciting, "useful for high energy therapeutic treatment, because the term "useful" is a subjective term that lacks a comparative basis for defining its metes and bounds.

Regarding claim 46, the term "such" renders the claim indefinite because it is unclear whether the "medicament" following the term "such" is the same as the first occurrence of the term "medicament" in the claim. Perhaps, Applicant intends the term, "the" or "said".

Claim 47 is vague and indefinite in reciting, "adapted for intracorporeal administration" because it is unclear how the pharmaceutical composition has been modified, i.e. adapted, for intracorporeal administration.

Claim 47 is vague and indefinite in reciting, "an effective amount" because the term "effective" is a subjective term that lacks a comparative basis for defining its metes and bounds.

In claims 48-50, "Claim" should be --claim--.

SCOPE OF ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-40 and 46-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a medicament or pharmaceutical composition which functions in combination with ionizing radiation for treating diseased cancer, infected, and lipocytic tissue, does not reasonably provide enablement for treating all other diseased tissue, such as vascular and nasal tissue, involved in coronary artery disease, myocardial infarction, and allergic reaction conditions,

respectively, as an example. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those skilled in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a medicament or a pharmaceutical composition comprising halogenated xanthenes used in combination with ionizing radiation for treating cancer or infected human and animal diseased tissue. Specifically, these halogenated xanthenes which exhibit high intrinsic radiodensity increase the therapeutic potential of ionizing radiation.

The state of the prior art- the prior art of record fails to disclose a medicament or a pharmaceutical composition comprising halogenated xanthene used in combination with ionizing radiation for treating any and all human and animal diseased tissue.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed medicament or pharmaceutical composition comprising halogenated xanthenes will work in treating any and all of human and animal

diseased tissue involving all conditions known to man upon application with ionizing radiation.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed medicament or pharmaceutical composition comprising halogenated xanthenes to work for treating cancer, lipocytic, and infected diseased tissue upon application with ionizing radiation. However, the specification fails to provide guidance to enable the claimed composition to function in treating any and all human and animal diseased tissue involving conditions affecting a majority of all organ systems.

The presence or absence of working examples- no working examples are provided in the specification that show the claimed medicament or pharmaceutical composition comprising halogenated xanthenes to work for treating any and all diseased human and animal tissue upon application with ionizing radiation which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the pharmaceutical composition capable of treating any and all diseased human and animal diseased tissue, as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a medicament or a pharmaceutical composition comprising halogenated xanthenes that is applicable for treatment of any and all of human and animal diseased tissues without any regard to the type of condition that a subject is inflicted with. As recited, the instant

medicament or pharmaceutical composition comprising halogenated xanthenes is capable of treating any and all human or animal tissue involving any disease condition.

As described in the specification at page 3, lines 19-20, radiodense medicaments or pharmaceutical compositions comprising halogenated xanthenes which are intracorporeally administered, function by enhancing absorption of applied ionizing radiation dose into sensitized (treated) tissues. These medicaments are specifically used for high-energy phototherapeutic treatment of tissue in diseased organ systems (pages 6 and 11). At page 5, lines 1-2, the specification provides that the radiosensitizer compositions, i.e. halogenated xanthenes, are also coupled with a biological targeting moiety to enhance concentration of the composition in diseased tissue. At page 7, lines 19-20 and page 13, however, the specification only refers to desirable effects after treatment with the composition and ionizing radiation, as including reduction, elimination, or eradication of diseased cancerous, precancerous, infected, i.e. having infectious agents such as bacteria or fungus or parasitic tissue, or undesirable lipocytic tissues, present in organ systems. As such, nowhere in the specification describes or exemplifies how a halogenated xanthene composition in combination with ionizing radiation can be used to treat any other diseased tissue such as cardiac tissue in myocardial infarct patients or diseased pancreatic tissue in diabetic patients, by eliminating or eradicating the supposed diseased portion of the tissues involved. The specification does not establish a direct correlation between cancerous, tumorous, infected, and lipocytic tissues with all other disease conditions in all humans and animals which would lead the skilled artisan to say that if the claimed composition works

for these aforementioned tissues and conditions involved therewith, then it should work in all other disease conditions in order to enable the breadth of the claimed composition. While it is not necessary to describe and exemplify every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed composition is enabled. This is not the case in the instant specification. Thus, the claimed composition is only enabled for medicaments or pharmaceutical compositions comprising halogenated xanthenes used in combination with ionizing radiation for treating cancerous, infected, and lipocytic diseased tissues and conditions involved, therewith.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed composition for treating any and all diseased tissues, would be great as 2) there is no experimental evidence provided that would indicate that the claimed composition would work for treating all diseased tissues, other than cancer, infected, or lipocytic tissue which are eliminated, reduced, or eradicated upon exposure to ionizing radiation; 3) there is no proper guidance that shows that treatment by elimination, reduction, or eradication of any diseased tissue, i.e. cardiac tissue, by the claimed composition can treat all disease conditions, i.e. myocardial infarct, in the instant specification, 4) the nature of the invention is a medicament or a pharmaceutical composition comprising halogenated xanthenes used in combination with ionizing radiation for treating cancer or infected human and animal diseased tissue; these halogenated xanthenes which exhibit

high intrinsic radiosensity increase the therapeutic potential of ionizing radiation, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows a medicament or a pharmaceutical composition comprising halogenated xanthene used in combination with ionizing radiation for treating any and all human and animal diseased tissue, and lastly 7) the claims broadly recite a medicament or a pharmaceutical composition comprising halogenated xanthenes that is applicable for treatment of any and all of human and animal diseased tissue, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1-40 and 46-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10, 14-15, 18-20, 51-52, 55-67, and 61-67 of copending Application No. 09/382,622, which is currently under appeal. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications claim a composition, a radiosensitizing agent, comprising halogenated xanthene as an active agent, used in combination with ionizing radiation, to treat diseased tissue by enhancing the effect of applied radiation upon the treated tissue.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 1-40 and 46-50 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 09/382,622 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if published or patented. This provisional rejection under 35 U.S.C. 103(a) is based upon a presumption of future publication or patenting of the conflicting application. Currently, claims 1-10, 14-15, 18-20, 51-52, 55-67, and 61-67 of copending Application No. 09/382,622, are under appeal.

Claims 1-10, 14-15, 18-20, 51-52, 55-67, and 61-67 of copending Application No. 09/382,622, differs from the instant invention in failing to disclose that the medicament or pharmaceutical composition or radiosensitizing agent, comprising halogenated

xanthenes used in combination with ionizing radiation can concentrate in and treat other diseased tissue such as infected and lipocytic tissue, which are eliminated, reduced, or eradicated, upon application of ionizing radiation upon the diseased tissue.

However, Applicant's disclosure provides that desired effects from treatment with the composition and ionizing radiation, includes reduction, elimination, or eradication of the specific diseased tissue; thus, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the composition upon undesired infected or lipocytic tissue so as to reduce, eliminate, or eradicate such tissue, as is done with cancerous, precancerous, or tumorous tissue, which may be present in specific organ systems because both disclosed inventions are generic with respect to the types of tissue that is treated by the sample.

This provisional rejection might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by a showing of a date of invention for the instant application prior to the effective U.S. filing date of the copending application under 37 CFR 1.131. For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The claimed invention is drawn to a medicament or a pharmaceutical composition *comprising* halogenated xanthene as a primary active component, which is used in combination with ionizing radiation, for phototherapeutic treatment of human or animal tissue. Accordingly,

7. Claims 1, 5-13, 15-17, 20-22, 25-26, 28-29, 33-40, 46-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Gulliya et al. (US 5,177,073

Gulliya et al. disclose a medicament or a pharmaceutical (therapeutic) composition comprising a photoactive compound that contains at least one chromophore for destroying tumor and pathogenic contaminants that infect animal body tissue. (see Abstract, column 4, line 43 to column 5, line 4). The medicament is activated by application of ionizing radiation, i.e. X-ray irradiation and gamma irradiation (see column 9, line 66 to column 10, line 20). The photoactive compounds are dyes which comprise chemical classes and derivatives which include xanthenes and which

may be halogenated. The photoactive compounds are dissolved and mixed with physiologically acceptable aqueous solutions, i.e. saline and electrolytes, which can be directly injected in vivo into tissue (see column 10, lines 26-44 and columns 15-16). The photoactive compound also has coupled thereto, a targeting moiety (conveyor) which is antibody or a matrix that is biocompatible and inert (see columns 7-8 and column 9, lines 10-37).

8. Claims 1, 3, 5, 8-12, 15-18, 20, 22-23, 25, 28-29, 31, 33, 36-39, 46-48, and 50 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975).

Serafini et al. teach a halogenated, i.e. iodinated, xanthene, in this case, Rose Bengal, which is principally tetrachlorotetraiodofluorescein. Rose Bengal allows for 1) rapid and efficient incorporation into molecules so as to attain overall reduction in imaging time and radiation exposure, and 2) improved images (see Abstract). Serafini et al. use the agent for treating diseased tissue as a radiopharmaceutical agent. In a study, Serafini et al. intravenously injected Rose Bengal into healthy volunteers, blood clearance and urinary clearance studies were performed, then simultaneous and sequential scintiphotos were taken of the cardiac, liver, biliary, and intestinal systems. It was found that sufficient concentration of Rose Bengal into diseased tissue, i.e. localization, within the liver then the rest of the biliary tree of the radiopharmaceutical agent is observed with marked improvement in anatomic detail showing specific areas of radioactive concentrations (see page 630, column 2).

9. Claims 1, 3, 5, 8-10, 12, 16, 18, 20, 22-23, 25, 28-29, 31, 33, 36-39, 46-48, and 50 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)).

Neckers teaches and describes halogenated xanthenes such as Rose Bengal or 2,4,5,7- tetraiodo-3', 4', 5', 6'- tetrachlorofluorescein. Neckers specifically teach that Rose Bengal and Eosin have distinct spectral, photochemical, and photophysical properties. Neckers teaches that Rose Bengal, disodium salt is characterized 1) as a photodynamic sensitizer, 2) by large absorption in all solvents, 3) by its capacity to be activated as an imaging agent, i.e. shows fluorescence, 4) by a triplet that is completely quenched by oxygen, 5) by its concentration on selected tissues, i.e. tumor: its spectrum is most diagnostic of its immediate environment, 6) by bleaching in protic, polar solvents, (7) by its singlet quenched by strong oxidizing agents (see page 1). The absorption and emission spectra of certain Rose Bengal derivatives are enumerated in Table 2 and 3, respectively.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 2, 27, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulliya et al. (US 5,177,073).

Gulliya et al. disclose a medicament or a pharmaceutical (therapeutic) composition comprising a photoactive compound that contains at least one chromophore for destroying tumor and pathogenic contaminants that infect animal body tissue. (see Abstract, column 4, line 43 to column 5, line 4). The medicament is activated by application of ionizing radiation, i.e. X-ray irradiation and gamma irradiation (see column 9, line 66 to column 10, line 20). The photoactive compounds are dyes which comprise chemical classes and derivatives which include xanthenes and which may be halogenated. The photoactive compounds are dissolved and mixed with physiologically acceptable aqueous solutions, i.e. saline and electrolytes, which can be directly injected in vivo into tissue (see column 10, lines 26-44 and columns 15-16). The photoactive compound also has coupled thereto, a targeting moiety (conveyor) .

which is antibody or a matrix that is biocompatible and inert (see columns 7-8 and column 9, lines 10-37).

Gulliya et al. differ from the instant invention in failing to disclose that halogenated xanthene is present in the concentration of 0.001% to less than 20%.

However, the concentration of halogenated xanthene in relation to the aqueous mixture to create the pharmaceutical composition, constitute result effective variables which Gulliya et al. have shown may be altered depending on the xanthene used and the tissue being treated in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the concentration range recited in instant claims 2, 27, and 30 are for any particular purpose or solve any stated problem and Gulliya et al. has shown that concentrations often vary according to the halogenated xanthene used and purpose of use thereof, and since such parameters appear to work equally as well, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of

the active ingredient concentrations disclosed by the prior art by normal optimization procedures.

11. Claim 4, 19, 24, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gulliya et al. (US 5,177,073) in view of Fondren et al. (Environ Entomol (1978)).

Gulliya et al. has been discussed supra. Gulliya et al. differ from the instant invention in failing to specifically disclose that the halogenated xanthene is tetrabromoerythrosin.

Fondren et al. enumerate six xanthene dyes and describe their relative toxicities. Specifically, Fondren et al. teach that xanthene dyes, among others include rose bengal, octabromofluorescein, erythrosin B, phloxin B, eosin Y, and tetrachlorofluorescein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute other halogenated xanthenes, such as tetrabromofluorescein, for the halogenated xanthenes taught in the teaching of Gulliya because tetrabromoerythrosin constitutes an obvious halogenated xanthenes which are routinely varied in the art and which have not been described as being critical to the practice of the invention.

12. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gulliya et al. (US 5,177,073) or Neckers D. (Journal of Photochemistry and Photobiology, A:

Chemistry 47: 1-29 (1989)) in view of Norman et al. (Invest Radiol, 26: S120-S121, 1991).

Gulliya et al. has been discussed supra.

Neckers teaches and describes halogenated xanthenes such as Rose Bengal or 2,4,5,7- tetraiodo-3', 4', 5', 6'- tetrachlorofluorescein. Neckers specifically teach that Rose Bengal and Eosin have distinct spectral, photochemical, and photophysical properties. Neckers teaches that Rose Bengal, disodium salt is characterized 1) as a photodynamic sensitizer, 2) by large absorption in all solvents, 3) by its capacity to be activated as an imaging agent, i.e. shows fluorescence, 4) by a triplet that is completely quenched by oxygen, 5) by its concentration on selected tissues, i.e. tumor: its spectrum is most diagnostic of its immediate environment, 6) by bleaching in protic, polar solvents, (7) by its singlet quenched by strong oxidizing agents (see page 1). The absorption and emission spectra of certain Rose Bengal derivatives are enumerated in Table 2 and 3, respectively.

Gulliya et al. and Neckers differ from the instant invention in failing to teach applying ionizing radiation at specifically greater than approximately 1 keV and less than approximately 1000 MeV.

Norman et al. teach pharmaceutical compositions that comprise iodinated contrast media such as gandolinium, for treatment of diseased tissue by applying ionizing radiation wherein doses absorbed from diagnostic X-rays are enhanced. Norman et al. specifically teach that the contrast media exhibit preference to localize at biologically sensitive diseased tumor tissues. Norman et al. also teach that dose

enhancement factor (DEF) which increases linearly with the concentration of halogen, i.e. iodine, can be achieved with other conventional ways of administering the contrast media (S120, column 1 and 2). Figure 1 shows a plot of the DEF as a function of the iodine concentration in a lymphocyte medium during irradiation at 140 keV. According to Norman et al., the therapeutic ratio, the ratio of radiation dose absorbed by a diseased brain tumor tissue versus that absorbed by the surrounding normal brain tissues increases with increasing contrast medium in the diseased tissue.

One of ordinary skill in the art at the time of the instant invention would have been motivated to activate the halogenated xanthene or Rose Bengal, taught by Gulliya and Neckers, with ionizing radiation at 140 keV as taught by Norman because Norman specifically taught applying ionizing radiation at 140 kEV upon gandolinium, which is a radiosensitizing agent which exhibits preference to localize at biologically sensitive diseased tumor tissues and the halogenated xanthene or Rose Bengal taught by Gulliya and Neckers, are obvious variations or modifications of a rediosensitizing agent upon which ionizing radiation can be applied for use in imaging, and which have been taught by Gulliya and Neckers as being characteristically capable of photodynamic and radiation activation.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703)

305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP 1800/1641

Gailene R. Gabel
October 20, 2002